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DOI:

[10.1016/j.bbi.2018.03.030](https://doi.org/10.1016/j.bbi.2018.03.030)

Document Version

Peer reviewed version

[Link to publication record in King's Research Portal](#)

Citation for published version (APA):

Danese, A. (2018). Developmental psychoneuroimmunology grows up. *Brain, Behavior, and Immunity*.
<https://doi.org/10.1016/j.bbi.2018.03.030>

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Accepted Manuscript

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PII: S0889-1591(18)30083-7
DOI: <https://doi.org/10.1016/j.bbi.2018.03.030>
Reference: YBRBI 3368

To appear in: *Brain, Behavior, and Immunity*

Received Date: 22 March 2018
Accepted Date: 23 March 2018

Please cite this article as: Danese, A., Developmental psychoneuroimmunology grows up, *Brain, Behavior, and Immunity* (2018), doi: <https://doi.org/10.1016/j.bbi.2018.03.030>

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Developmental psychoneuroimmunology grows up

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Word count=999

Reference count=10

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How is childhood stress translated into biological risk for disease? Childhood stressors like abuse or bullying are arguably the top modifiable causes of mental illness (Sara & Lappin 2017). Furthermore, childhood stress may affect risk for medical conditions, such as cardiovascular and metabolic disorders (Suglia et al. 2018). The mechanisms underlying the enduring effects of childhood stress are, however, poorly characterised, and this has delayed the identification of targets for secondary prevention - namely strategies to stop underlying biological processes linked to child stress before the onset of clinical symptoms. Increasingly, research suggests that the immune system - and particularly the inflammatory response - may help explain the detrimental health consequences of childhood stress (Danese & Lewis 2017; Nusslock & Miller 2016). In the past decade, several epidemiological studies explored this hypothesis by testing the association between childhood stressors and peripheral inflammatory biomarkers in humans.

Chen and Lacey (Chen & Lacey 2018) make a helpful addition to this literature. The authors took advantage of data from the 1958 British birth cohort, a population-representative cohort of 17,000 newborns born in a single week in 1958 and followed up till adulthood. Study members were comprehensively assessed on their psychosocial environment as they grew up and throughout their lives. At age 45 (2003), a biomedical data collection was undertaken on more than 9,000 study member enabling measurement of inflammation biomarkers. Capitalising on this data, Chen and Lacey (Chen & Lacey 2018) focused their analysis on a broad measure of childhood adversity (i.e., care placement, physical neglect, parental separation, family history of offences, mental illness, domestic conflict and alcohol misuse across childhood). The authors tested if childhood adversity was associated with inflammation biomarkers measured in adult life, and explored potential mechanisms accounting for such association. Their analyses offer important insights.

The association between childhood adversity and adult inflammation was observed in a longitudinal-prospective study. The longitudinal design enabled the authors to capitalise on a prospective measure of childhood adversity. This is remarkable because most of the three dozen epidemiological studies undertaken so far on this topic have relied on retrospective reports of childhood adversity by adult participants, owing to the greater feasibility of collecting such measures (retrospective reports do not require extensive data collection over several years and, thus, are quicker and cheaper). However, the interpretation of findings based on retrospective reports is ambiguous because retrospective and (presumably more valid) prospective measures of childhood adversity identify largely non-overlapping groups of individuals (Reuben et al. 2016). Along with our work in the Dunedin Study (Danese et al. 2007) and findings in the ALSPAC Study (Slopen et al. 2013), the paper by Chen and Lacey (Chen & Lacey 2018) suggests that adult inflammation is associated with prospective as well as retrospective measures of childhood adversity. It also suggests that the association does not simply emerge because of biased reports by adults with high inflammation levels. This is an important observation because psychiatric disorders associated with high inflammation levels, such as depression, may affect reporting due to negative biases in autobiographical memory (Reuben et al. 2016). The findings, therefore, reassure us that the apparent links between childhood adversity and inflammation in humans do not simply reflect measurement bias.

The association between childhood adversity and adult inflammation was not explained by key potential confounders measured. Rigorous modelling of potential confounders is critical in observational studies because children are clearly not randomly allocated to adversity. Consequently, children who do or do not experience adversity often differ on several features, some of which may also affect adult inflammation. Any such group differences offer alternative explanations for the observed associations between childhood adversity and adult inflammation and, thus, should be accounted for. The comprehensive prospective assessment undertaken in the 1958 British cohort enabled the authors to statistically model the ef-

fects of several features correlated with childhood adversity, including the children's broader socio-economic environment and their health in early life. The findings by Chen and Lacey (Chen & Lacey 2018), therefore, reassure us that the apparent links between childhood adversity and inflammation in humans do not simply reflect confounding bias owing to socio-economic conditions or health in early life. Nevertheless, even in this comprehensive dataset, causal inference is limited by the availability of information: variables not measured in this dataset might still confound the association and need to be studied further. For example, we have recently tested in the E-Risk Longitudinal Twin Study whether the association between childhood victimisation and adult inflammation emerges because of higher genetic liability to inflammation in victimised children, and found limited evidence of confounding (Baldwin et al. 2018). Although more research is needed to strengthen causal inference in humans, causal effects have been repeatedly described within animal models of early life stress (Danese & Lewis 2017).

The association between childhood adversity and adult inflammation was explained by psychosocial and behavioural pathways. Better understanding of the pathways through which childhood stress affects inflammation (Danese & Lewis 2017) is needed to buffer detrimental health consequences. In addition to the often studied biological pathways involving the hypothalamic-pituitary-adrenal axis and the peripheral nervous system, the study by Chen and Lacey (Chen & Lacey 2018) highlights that psychosocial and behavioural pathways are relevant to explain the links between childhood adversity and adult inflammation in humans. Of course, it is possible that psychosocial measures like low educational achievement or behavioural measures like smoking are overt manifestations of detrimental biological effects of childhood adversity on the brain - thus ultimately reflecting biological mechanisms. However, regardless of their origins, both low educational achievement and smoking may perpetuate high inflammation levels and, thus, can be helpful targets for interventions. Formal mediation modelling in longitudinal datasets will be helpful to further explore relevant pathways.

In conclusion, the paper by Chen and Lacey (Chen & Lacey 2018) is a good example of how the field of developmental psychoneuroimmunology is growing in depth and breadth from initial experiments in animal models (Danese 2014) - asking increasingly more complex and challenging questions in search of its own (translational) significance.

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